SECTION I
INFRASTRUCTURE

1 The U.S. Food and Drug Administration and the regulation of small molecules for orphan diseases

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THE ORPHAN DRUG ACT

Responding to heightened public appeal by a coalition of patient representatives, Representative Henry Waxman introduced into the United States Congress, in 1981, legislation to address the lack of interest in the pharmaceutical sector to develop drugs for rare but often serious or fatal diseases.[1] These "orphan" diseases do not present sufficiently viable markets for drug makers to recover the drug-development costs, much less to expect profitability. In December 1982, Congress passed the Orphan Drug Act ("the Act") amending the Federal Food, Drug, and Cosmetic Act (FDCA) to establish incentives for the development of promising drugs for rare diseases or conditions in the United States. On January 4, 1983, President Ronald Reagan signed the Act into law.[2] To implement the provisions

of the Act, the United States Food and Drug Administration (FDA) issued the Orphan Drug Regulations Final Rule in 1992.[3]

WHAT ARE THE ORPHAN DRUG INCENTIVES?

The Act initially defined an orphan drug on the basis of unprofitability: one intended for the diagnosis, treatment, or prevention of a rare disease or condition in the United States, such that there was no reasonable expectation that the costs of developing the drug would be recovered from its sales in the United States. This definition was amended in 1984 to provide, in addition, a prevalence threshold of 200,000 persons affected by the disease or condition of interest in the United States as a surrogate for the lack of profitability. The Act, as amended, provided financial and regulatory incentives to encourage the development of potentially promising orphan drugs as discussed below.

Orphan drug marketing exclusivity

This is the most important incentive of the Act. After the FDA has approved the orphan drug for marketing, the drug sponsor receives a seven-year exclusivity period for the rights to market the drug for the approved orphan indication.[4] That is, during this period, the FDA may not approve another same drug for the same indication (see the section "How Does the FDA Protect the Marketing Exclusivity of the Pioneer Drug?" for further discussion on the protection of marketing exclusivity). Exclusivity may be withdrawn by the FDA only if the sponsor fails to assure an adequate supply of the drug to meet the needs of patients. In this instance, which has never occurred, the marketing approval status of the drug would not be affected.

Orphan products grants

The Orphan Products Grants Program is administered by the FDA Office of Orphan Products Development (OOPD).[5] Its objective is to provide seed money for clinical investigations on the safety and effectiveness of drugs, medical devices, and medical foods for the diagnosis, treatment, and prevention of rare diseases or conditions in the United States. Grants are awarded on a competitive basis to foreign or domestic, private or public, for-profit or not-for-profit, state or local units of government, and federal agencies (not part of the Department of Health and Human Services). In fiscal year 2009, a Phase I clinical study is eligible for grant support of up to $200,000 per year for a period of three years, and Phase 2, 3, and 4 clinical investigations (see the section "How Has the FDA Approved Nonbiological Orphan Drugs for Genetic Disorders?" for explanations on phases of drug development) may be eligible for support of $400,000 per year for up to four years.[6] Except for medical foods, clinical investigation on a drug or a medical device supported by orphan product grants must be conducted under

an approved Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) application, respectively.

Written recommendations for investigation of an orphan drug

The FDA, upon request, will issue written recommendations to the sponsor of an orphan drug for the nonclinical (in vitro and in vivo laboratory animal testing) and clinical drug research and development programs necessary for the drug's approval. This regulatory incentive – initially intended for orphan drugs – has been replaced by the FDA-wide informal consultation process known as the pre-IND program.[7]

Open protocols for investigation of orphan drugs

The sponsor of an orphan drug under clinical investigation is encouraged to expand the *treatment use* of the drug to patients who are not eligible to be in the clinical trials and who cannot be satisfactorily treated by available alternative drugs. Such expanded use is governed by the regulations on treatment use protocol of an IND.[8] To initiate such an open protocol, the sponsor must demonstrate to the FDA that (1) the disease or condition is serious or immediately life-threatening, (2) the drug is under active clinical investigation with sufficient evidence of safety and effectiveness, and (3) there is no comparable or satisfactory alternative therapy.

Tax credit

The sponsor of the orphan drug can claim an orphan drug tax credit against federal taxes equal to 50% of the clinical testing expenses incurred between the date the drug is designated as an orphan drug by the FDA and the date of its marketing approval.[9,10] To be eligible, the clinical testing must be conducted under an approved IND. The tax credit may apply to foreign clinical investigation expenses if there is an insufficient testing population in the United States. As currently allowed, the unused tax credit can be carried back one year and then forward 20 years.

Waiver of user fees

In 1992, Congress passed the Prescription Drug User Fee Act authorizing the FDA to collect user fees from drug sponsors to support the costs of drug reviews in exchange for FDA agreement to meet drug-review performance goals in a timely fashion.[11] These fees include the application fee levied on the sponsor's New Drug Application (NDAs) for marketing approval of the drug, the annual establishment fee, and the product fee. Subsequently, the Food and Drug Administration Modernization Act of 1997 exempted sponsors of designated orphan drugs from the application fee. The Food and Drug Administration Amendments Act (FDAAA)

of 2007 further allowed exemption of the establishment fee and product fee, if the sponsor's gross worldwide revenue is less than $50 million in the preceding year.[12,13] These exemptions represent substantial financial incentives. For example, the application fee, establishment fee, and product fee in 2009 each amount to $1,247,200, $425,600, and $71,520, respectively. These fees continue to increase annually.

HOW DOES A SPONSOR SEEK AND OBTAIN ORPHAN DRUG DESIGNATION?

To be eligible for the aforementioned incentives, a sponsor must submit to the OOPD a request for orphan drug designation of a drug previously unapproved for the rare disease or condition of interest.[14] The OOPD, an office located in the FDA's Office of the Commissioner, administers the Act. The request can now be submitted electronically.[15] As of May 2008, sponsors of orphan drugs may also use a common application form to submit their designation requests to the FDA and the European Medicines Agency (EMEA).[16] The request to the FDA must contain the following information:

- the sponsor's contact information (or the authorized United States resident agent if the sponsor is not a United States–based entity);
- the generic and trade name (if available) of the drug;[17]
- the formulation, chemical and physical properties, proposed dosage form, and route of administration;
- the contact information of the drug's manufacturer;[18]
- the proposed orphan designation;
- a description of the rare disease or condition in question;
- the reasons why the drug is needed;
- the scientific basis for the use of the drug;[19]
- for a treatment drug, documentation showing that the rare disease or condition affects fewer than 200,000 persons in the United States at the time the request is submitted;[20,21]
- for a diagnostic drug, preventive drug, or a vaccine, documentation showing that the number of persons to whom the drug may be administered annually is less than 200,000;
- if the prevalence *exceeds* the statutory threshold of 200,000 persons, documentation to support the lack of reasonable expectation on cost recovery, even if the drug is solely marketed in the United States for seven years;
- a summary of the regulatory history and development status of the drug; and
- a statement attesting that the sponsor is the real party of interest in the development, production, and sales of the orphan drug.

The designation request may be submitted to the FDA at any time during the drug-development process, preferably before the commencement of clinical

investigation to maximize the tax credit benefit. It must, however, be filed before the sponsor submits its own marketing application of the drug.[22] Until such orphan drug is approved, another sponsor may file a separate designation request for the same drug for the same use.

An orphan designation, after being granted, may be revoked only if the FDA later finds material facts that the drug was ineligible for orphan designation at the time the sponsor submitted the request.[23] To protect the sponsor from unpredictable investment risks, the designation status cannot be revoked even if the prevalence of the disease or condition (e.g., because of an outbreak or advancement in diagnosis) subsequently surpasses the threshold of 200,000.[24] At any time before the drug is approved, the sponsor may request an amendment to the designation on the basis of unexpected findings, if such amendment does not render the drug ineligible for orphan designation.[25]

WHAT IS A MEDICALLY PLAUSIBLE SUBSET?

In general, an orphan designation is granted to a drug intended for use by all patients with a rare disease or condition. Nevertheless, the Orphan Drug Regulations also stipulate that a drug may be designated for use in a defined subset of patients with a *common* disease or condition, provided that the sponsor can plausibly demonstrate that the drug will be developed for use solely in that subset – in other words, the remaining patients are not appropriate candidates for the drug.[26] The subset is often referred to, in regulatory parlance, as a *medically plausible subset*.[27]

Medically plausible subsets have been legitimately defined by the drug's toxicity profile (e.g., a toxic drug to be used in only patients refractory to all lesser toxic treatments); mechanism of action (e.g., a receptor-specific drug for use in receptor-positive patients); unique biopharmaceutical property (e.g., a prodrug requiring metabolic conversion in responders to be effective); route of administration (e.g., an inhalation drug to treat lung-transplant rejection); or previous clinical experiences (e.g., clinical trials showing the drug to be safe and effective in only adult patients). It is reasonable to expect also that a drug targeting a rare genotype-encoded mutation of a common disease phenotype may qualify for orphan designation for the subset of individuals affected by the mutation. In recognizing pediatric patients as "therapeutic orphans," the OOPD has, for years, granted orphan designation to drugs without approved pediatric indication to spur the development of drugs for use in this population.[28]

HOW DOES THE FDA PROTECT THE MARKETING EXCLUSIVITY OF THE PIONEER DRUG?

Under the Orphan Drug Regulations, two drugs are considered the same if they contain the same active substance (i.e., the *active moiety* of a small-molecule drug,

or the *principal molecular structural feature* of a large-molecule drug.[29] These regulatory stipulations are solely intended to maximize exclusivity protection to the first approved orphan drug. For example, a second sponsor can neither produce a new salt or an ester form of the same active moiety nor introduce a different glycosylation pattern of a protein drug – a relatively insignificant undertaking in either case – to circumvent the first sponsor's orphan drug exclusivity.

Nevertheless, the Orphan Drug Regulations allow orphan designation of a newly developed drug containing the same active substance as a previously approved drug for the same rare disease or condition, if the sponsor of the newly developed drug can present a *plausible hypothesis* that the former is *clinically superior* to the latter.[30] This provision was put forth to encourage the development of better orphan drugs and to advance public health. Clinical superiority may be based on greater safety, greater effectiveness, or, when neither can be shown, the drug making a major contribution to patient care.[31] The marketing approval of such a drug, however, is conditioned upon definitive evidence of clinical superiority. If this superiority is proven, the sponsor will receive the seven-year marketing exclusivity for this drug.

It is notable that an orphan drug sponsor, despite marketing exclusivity for the orphan indication, may still be vulnerable to marketing competition. This situation may occur when one or more comparable generic versions of the protected drug already exist on the market for other, nonorphan indications. Although the FDA will not permit generic drugs to be labeled for the exclusive orphan indication, the existence of the generic version of the product may not prevent off-label use of the possibly less-expensive versions of the protected drug for the same indication.

OVERVIEW OF NONBIOLOGICAL ORPHAN DRUGS APPROVED FOR GENETIC DISORDERS

As of March 2009, the FDA has approved 24 nonbiological orphan drugs for 21 indications related to genetic disorders (Table 1–1). Sixteen (67%) drugs were considered to be *new molecular entities* – innovator drugs that had not been previously approved by the FDA for any other uses (Table 1–2). The prevalence of the diseases or conditions of interest at the time the sponsor made the orphan-designation request ranged from several hundred to 127,000 persons (median ~15,000). The rate of FDA marketing approval was, on average, one drug per year (Figure 1–1). The FDA also granted priority review of marketing application to the majority (80%) of these drugs.[32]

Of the 21 indications, 17 (81%) are for treatment or management of the disease or condition, three (14%) for preventive use, and one (5%) for diagnostic purposes. One drug was concurrently approved for dual indications: desmopressin for treatment of hemophilia A and for von Willebrand disease type I.

Of the 24 approved drugs, Ucephan (sodium benzoate and sodium phenylacetate) and synthetic porcine secretin are no longer available on the market. The

Table 1–1. Nonbiological orphan drugs approved by the FDA for genetic disorders

Generic name	Trade name	Source*	Indication
Ambrisentan	LETAIRIS®	Gilead Sciences	Treatment of pulmonary arterial hyp
Apomorphine	APOKYN®	Vernalis Pharmaceuticals	Treatment of off episodes in Parkinso
Benzoate/phenylacetate	UCEPHAN®	Kendall McGaw Pharmaceuticals	Treatment/prevention of hyperammo
Benzoate/phenylacetate	AMMONUL®	Ucyclyd Pharma	Treatment of acute hyperammonemi
Betaine	CYSTADANE®	Jazz Pharmaceuticals	Treatment of homocystinuria
Bosentan	TRACLEER®	Actelion Pharmaceuticals	Treatment of pulmonary arterial hyp
Cysteamine	CYSTAGON®	Mylan Pharmaceuticals	Treatment of nephropathic cystinosis
Desmopressin	DDAVP®	Sanofi Aventis	Treatment of hemophilia A/von Wille
Epoprostenol	FLOLAN®	GlaxoSmithKline	Treatment of pulmonary arterial hyp
Iloprost	VENTAVIS®	Actelion Pharmaceuticals	Treatment of pulmonary arterial hyp
Levocarnitine	CARNITOR®	Sigma-Tau Pharmaceuticals	Treatment of primary carnitine defici
Miglustat	ZAVESCA®	Actelion Pharmaceuticals	Treatment of type 1 Gaucher disease
Nitisinone	ORFADIN®	Rare Disease Therapeutics	Treatment of hereditary tyrosinemia
Riluzole	RILUTEK®	Sanofi Aventis	Treatment of amyotrophic lateral scl
Sapropterin	KUVAN®	BioMarin Pharmaceutical	Treatment of hyperphenylalaninemia
Selegiline	ELDEPRYL®	Somerset Pharmaceuticals	Adjunct treatment of Parkinson disea
Synthetic porcine secretin		*ChiRho*Clin	Diagnosis of gastrinoma
Phenylbutyrate	BUPHENYL®	Medicis	Chronic adjunctive treatment of hype
Tiopronin	THIOLA®	Mission Pharmacal	Prevention of cystine stone in homoz
Tobramycin	TOBI	Novartis Pharmaceuticals	Management of CF patients with *Pseu*
Tranexamic acid	CYKLOKAPRON®	Pfizer	Prevention of tooth-extraction hemor
Treprostinil	REMODULIN®	United Therapeutics	Treatment of pulmonary arterial hyp
Trientine	SYPRINE®	Aton Pharma	Treatment of penicillamine-intolerant
Zinc acetate	GALZIN®	Gate Pharmaceuticals	Maintenance treatment of Wilson dis

* Last known source (as of March 2009). UCD: urea cycle disorders; AIP: acute intermittent porphyria; CF: cystic fibrosis.

Table 1–2. Timeline of orphan drug designation and marketing approval

Drug	Date of orphan designation	Date of marketing approval	Marketing application review*	Exclusivity status as of March 2009
Ambrisentan	7/16/2004	6/15/2007	P	Yes
Apomorphine	4/22/1993	4/20/2004	P	Yes
Benzoate/phenylacetate‡	1/21/1986	12/23/1987	P	No
Benzoate/phenylacetate	11/22/1993	2/17/2005	P	Yes
Betaine	5/16/1994	10/25/1996	P	No
Bosentan	10/6/2000	11/20/2001	S	No
Cysteamine	1/25/1991	8/15/1994	P	No
Desmopressin	1/22/1991	3/7/1994	P	No
Desmopressin	1/22/1991	3/7/1994	P	No
Epoprostenol	9/25/1985	9/20/1995	P	No
Iloprost	8/17/2004	12/29/2004	P	Yes
Levocarnitine	2/28/1984	4/10/1986	P	No
Miglustat	5/29/1998	7/31/2003	S	Yes
Nitisinone	5/16/1995	1/18/2002	P	No
Riluzole	3/16/1993	12/12/1995	P	No
Sapropterin	1/29/2004	12/13/2007	P	Yes
Selegiline	11/7/1984	6/5/1989	S	No
Synthetic porcine secretin‡	6/18/1999	4/4/2002	P	Yes
Phenylbutyrate	1/22/1993	4/30/1996	P	No
Tiopronin	1/17/1986	8/11/1988	P	No
Tobramycin	10/13/1994	12/22/1997	P	No
Tranexamic acid	10/29/1985	12/30/1986	S	No
Treprostinil	6/4/1997	5/21/2002	P	Yes
Trientine	12/24/1984	11/8/1985	P	No
Zinc acetate	11/6/1985	1/28/1997	S	No

* P: priority review; S: standard review (see text for explanation).
† Time rounded to the nearest month/year.
‡ No longer available on the market.

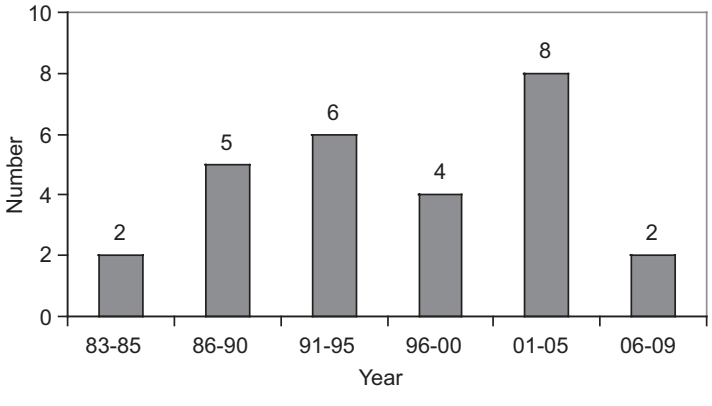

Figure 1–1: Number of biological orphan drugs approved by the FDA for genetic disorders over time.

remaining 22 orphan drugs are currently made available by 19 sponsors – six (27%) of which (Actelion Pharmaceuticals, Allschwil/Basel, Switzerland; Gilead Sciences, Foster City, CA: GlaxoSmithKline, Brentford, Middlesex, United Kingdom; Novartis Pharmaceuticals, Basel, Switzerland; Pfizer, New York, NY; and Sanofi Aventis, Bridgewater, NJ) are among the top 20 pharmaceutical or biotechnology companies ranked by sales in 2008.[33]

At the time this chapter was written, seven (32%) orphan drugs still retained orphan drug marketing exclusivity for the orphan indication (Table 1–2). Of the remaining 15 (68%) drugs with expired exclusivity, 9 (60%) currently have no competitive sources. Among the six drugs with generic counterparts, it is notable that three are relatively costly (epoprostenol – approximately $100,000/year; riluzole – approximately $9,600/year; and desmopressin – approximately $600/dose), two have other approved uses (desmopressin and levocarnitine), and one shares a growing target population (selegiline).[34,35,36] The seeming lack of interest by pharmaceutical manufacturers to offer generic versions of relatively unprofitable orphan drugs following the expiration of their exclusivity underlines the need for incentives not only for development, but also for assurance of their long-term marketing availability.

The time from orphan designation to marketing approval of the orphan drugs of interest varied greatly, from as short as 4 months 13 days for iloprost to as long as 15 years 2 months for miglustat (Table 1–2). The median time was approximately three years one month. This length of time may closely approximate how long it took for clinical testing of these drugs , because, for the most part, orphan designation occurred early in the clinical development phase. The actual overall time for a drug-development program (nonclinical and clinical testing) would be substantially longer. As stated earlier, the request for designation must be received by the OOPD prior to the receipt of the NDA by the FDA Review Division of the marketing application of the drug.

Several of these drugs were approved for the treatment of manifestations common to both genetic and nongenetic forms of the disease: ambrisentan, bosentan,